REM- 4887

123937

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 6-6-04
Art Unit: 1614 Phone Number ~~30~~ 272-0587 Serial Number: 10/018,235
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

A method for maintaining or improving the visual acuity and field vision in a patient with drug containing an inhibito of the enzyme that converts angiotensin I to angiotensin II.

The inhibitors is selected from

Ramipril
Ramiprilat
Captopril
Enalaprilat

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: _____	NA Sequence (#)_____		STN _____	
Searcher Phone #: _____	AA Sequence (#)_____		Dialog _____	
Searcher Location: _____	Structure (#)	_____	Questel/Orbit _____	
Date Searcher Picked Up: _____	Bibliographic	_____	Dr.Link _____	
Date Completed: _____	Litigation	_____	Lexis/Nexis _____	
Searcher Prep & Review Time: _____	Fulltext	_____	Sequence Systems _____	
Clerical Prep Time: _____	Patent Family	_____	WWW/Internet _____	
Online Time: _____	Other	_____	Other (specify) _____	

PTO-1590 (1-2000)

STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 123937

TO: Kevin Weddington
Location: REM-4B87/4C70
Art Unit: 1614
Wednesday, June 09, 2004

Case Serial Number: 123937

From: Mary Jane Ruhl
Location: Biotech-Chem Library
Remsen 1-B55
Phone: 571-272-2524

maryjane.ruhl@uspto.gov

Search Notes

Examiner Weddington,

Here are the results for your recent search request.

Please feel free to contact me if you have any questions about these results.

Thank you for using STIC services. We appreciate the opportunity to serve you.

Sincerely,

Mary Jane Ruhl
Technical Information Specialist
STIC
Remsen 1-A-62
Ext. 22524

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     FILE 'HCAPLUS' ENTERED AT 10:04:22 ON 09 JUN 2004
L1             1 SEA ABB=ON  REKIK RAOUF/AU
                 SELECT RN L1 1

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                 OR 9015-82-1/BI)

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L3             1 SEA ABB=ON  L1 AND L2

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L7             1 SEA ABB=ON  ENALAPRILAT/CN
L8             1 SEA ABB=ON  ANGIOTENSIN I/CN
L9             1 SEA ABB=ON  ANGIOTENSIN II/CN

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L11            3 SEA ABB=ON  L10 AND (?VISION? OR ?VISUAL?(W)?ACUITY? OR
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L12            3 SEA ABB=ON  L10 AND (?VISION? OR ?VISUAL?(W)?ACUITY? OR
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L13              ANALYZE L3 1- CT :        6 TERMS
L14         8466 SEA ABB=ON  (L4 OR L5 OR L6 OR L7 OR ?RAMIPRIL? OR ?RAMIPRILAT?
                  OR ?CAPTOPRIL? OR ?ENALAPRILAT?)
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L16           10 SEA ABB=ON  L15 AND (?VISION? OR ?VISUAL?(W)?ACUITY? OR
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L17           10 SEA ABB=ON  L16 AND ?INHIBIT?
L18           10 SEA ABB=ON  L16 OR L17  10 cits from CA Plus

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L19           59 SEA ABB=ON  L17
L20           37 DUP REMOV L19 (22 DUPLICATES REMOVED)  37 cits from other databases
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L8            1 SEA FILE=REGISTRY ABB=ON  ANGIOTENSIN I/CN
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                Y? OR EYE?)(L)(?IMPROV? OR ?ENHANC? OR ?INCREAS?)
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L18          10 SEA FILE=HCAPLUS ABB=ON   L16 OR L17

=> d ibib abs l18 1-10

L18  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2004:11030  HCAPLUS
DOCUMENT NUMBER:         140:270099
TITLE:                   Angiotensin converting enzyme (ACE) activity
                         in porcine ocular tissue: Effects of diet and ACE
                         inhibitors
AUTHOR(S):               Geng, Lijun; Persson, Karin; Nilsson, Siv F. E.
CORPORATE SOURCE:        Faculty of Health Science, Division of Pharmacology,
                         Department of Medicine and Care, Linkoeping
                         Universitet, Linkoeping, Swed.
SOURCE:                  Journal of Ocular Pharmacology and Therapeutics
                         (2003), 19(6), 589-598
                         CODEN: JOPTFU; ISSN: 1080-7683
PUBLISHER:               Mary Ann Liebert, Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The angiotensin converting enzyme (ACE) activity was measured in
     different parts of the eye in female minipigs. The effects of
     atherogenic 1% cholesterol diet on eye ACE activity were also
     evaluated. The pigs were fed standard (control) or high-cholesterol diet from
     30 to 63-75 wk of age. The eyes were enucleated and dissected
     into iris, ciliary body, retina, and choroid. Crude tissue homogenates
     were analyzed for ACE activity by radioenzymic assay. In pigs fed normal
     standard diet, the basal ACE activity was 18.1±1.6, 13.6±1.9,
     4.4±0.6, and 44.7±8.5 units/mg in the iris, ciliary body, retina,
     and choroid, resp. The ACE activities in ocular tissues from the pigs fed
     the atherogenic diet were not much different from controls, nor was the
     ACE activity in the abdominal aorta and blood serum. In both groups, the
     ACE inhibitors captopril and enalaprilat
     inhibited the ACE activity in the choroid and ciliary body, with
     enalaprilat being more potent. In the retina, the ACE activity
     was inhibited only in pigs fed the normal diet, whereas the ACE
     activity in the iris was not much inhibited in either group.
     Thus, no differences in ACE activity between pigs fed normal diet and
     atherogenic diet were found, which is in disagreement with previous
     studies that showed increased ACE activity in the aorta from
     atherosclerotic minipigs. The reason for the discrepancy is not clear,
     but lower cholesterol levels are a possibility.
REFERENCE COUNT:         39   THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18  ANSWER 2 OF 10  HCAPLUS  COPYRIGHT 2004 ACS on STN
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ACCESSION NUMBER: 2000:900442 HCAPLUS
DOCUMENT NUMBER: 134:37048
TITLE: Neuroprotective and retinoprotective ophthalmologic medicines
INVENTOR(S): Rekik, Raouf
PATENT ASSIGNEE(S): Rekik, Elyes Ben Mohamed Raouf, Fr.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000076499	A2	20001221	WO 2000-FR1679	20000616
WO 2000076499	A3	20010517		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2794975	A1	20001222	FR 1999-15359	19991206
BR 2000011714	A	20020305	BR 2000-11714	20000616
EP 1185255	A2	20020313	EP 2000-951603	20000616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200103665	T2	20021021	TR 2001-20010366520000616	
JP 2003501461	T2	20030114	JP 2001-502832	20000616
FR 2826276	A1	20021227	FR 2001-8136	20010620
NO 2001006088	A	20020212	NO 2001-6088	20011213

PRIORITY APPLN. INFO.:
TN 1999-99122 A 19990616
FR 1999-15359 A 19991206
WO 2000-FR1679 W 20000616

AB The invention concerns a neuroprotective and retinoprotective medicine, whereof the active principle is selected among a group of compds. consisting of **ramipril**, **ramiprilat** or any other **ramiprilat** derivative capable of releasing it in the organism whereto it is administered. Said medicine is used for prevention, or even for **improving visual acuity** and visual field in normal subjects, as well as for treating ophthalmol. pathologies involving a vascular factor, in particular glaucomatous neuropathy, degenerative choriopathy of strong myopia, age-related maculopathy, serous central chorioretinopathy, hereditary dystrophy of the retina and retinal venous occlusions. It almost invariably **improves** the visual function (acuity and visual field). Efficacy of 1.25 mg oral **ramipril** in the treatment of patients suffering from retinitis pigmentosa and dystrophy pseudo-vitelliform of adult was shown.

L18 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:390803 HCAPLUS
DOCUMENT NUMBER: 133:261319
TITLE: Short-term **angiotensin** converting enzyme **inhibition** reduces basal tone and dilator reactivity in skeletal muscle arterioles
AUTHOR(S): Frisbee, Jefferson C.; Lombard, Julian H.

CORPORATE SOURCE: Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
'SOURCE: American Journal of Hypertension (2000), 13(4, Pt. 1), 389-395
CODEN: AJHYE6; ISSN: 0895-7061
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alterations in resting tone, maximum diameter, and dilator reactivity to acetylcholine (ACH) and sodium nitroprusside (SNP) were assessed in cremaster muscle microvessels of Sprague-Dawley rats receiving **angiotensin** converting enzyme (ACE) **inhibition** with **captopril** for 4 days and in untreated time-control rats. The transilluminated in situ cremaster muscle was superfused with physiol. salt solution (PSS) and viewed via **television** microscopy; arteriolar diameter was measured using a video micrometer. Before agonist challenge, resting arteriolar diameter was significantly **increased** in **captopril**-treated rats. Although maximum arteriolar diameter (determined during superfusion of the cremaster muscle with Ca2+-free PSS containing 10-4 mol/L adenosine) was not altered with ACE **inhibition**, the maximum possible arteriolar dilation was reduced in **captopril**-treated rats. **Captopril** administration reduced both ACH- and SNP-induced dilation of cremaster IC arterioles compared with responses in control rats, although this was partially a function of the reduced capacity for dilation, primarily to SNP. These observations indicate that short-term ACE **inhibition** reduces both resting tone and agonist-induced dilator responses of skeletal muscle arterioles.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:768863 HCAPLUS
DOCUMENT NUMBER: 132:59404
TITLE: Central administration of the somatostatin analog octreotide induces **captopril**-insensitive sleep responses
AUTHOR(S): Beranek, L.; Hajdu, I.; Gardi, J.; Taishi, P.; Obal, F., Jr.; Krueger, J. M.
CORPORATE SOURCE: Department of Physiology, A. Szent-Gyorgyi Medical University, Szeged, 6720, Hung.
SOURCE: American Journal of Physiology (1999), 277(5, Pt. 2), R1297-R1304
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of intracerebroventricular injections of the long-lasting somatostatin analog octreotide (Oct) were studied on sleep and behavior in rats. Pyrogen-free physiol. saline and Oct (0.001, 0.01, 0.1 μg) or vehicle were administered at light onset, and the EEG, motor activity, and cortical brain temperature were recorded during the 12-h light period. Plasma growth hormone (GH) concns. were measured in samples taken at 30-min intervals after Oct. Oct (0.01 and 0.1 μg) suppressed non-rapid **eye** movement sleep (NREMS) for 1-2 h. NREMS intensity (delta EEG activity during NREMS) dose dependently **increased** in hour 3 postinjection and thereafter (0.1 μg). Plasma GH concns. were suppressed after Oct (0.01 and 0.1 μg), but pulses of GH secretions occurred 90-120 min postinjection in each rat. Oct (0.1 μg) **enhanced** behavioral activity, including prompt drinking followed by grooming, scratching, and feeding. Intracerebroventricular injection

of the **angiotensin**-converting enzyme **inhibitor** **captopril** (30 μg, 10 min before Oct), blocked these behavioral responses but not the Oct-induced sleep alterations. The changes in sleep after intracerebroventricular Oct suggest an intracerebral action site and might result from Oct-induced variations in the sleep-promoting activity of GH-releasing hormone.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:535717 HCAPLUS
DOCUMENT NUMBER: 129:153226
TITLE: Lacrimation enhancers containing ACE **inhibitors** for treatment of corneal and conjunctival diseases
INVENTOR(S): Nakada, Katsuhiko; Nakamura, Masatane
PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 3 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10218792	A2	19980818	JP 1997-27642	19970212

PRIORITY APPLN. INFO.: JP 1997-27642 19970212

AB Lacrimation **enhancers**, useful for treatment of dry **eye** , desquamation of corneal epithelial cell, and corneal ulcer, contain ACE **inhibitors** as active ingredients. **Enalaprilat** at 10-4 mol **increased** tear secretion in isolated rabbit lacrimal gland.

L18 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:786084 HCAPLUS
DOCUMENT NUMBER: 123:218345
TITLE: Effect of **captopril** on ocular irritative response to topical neutral formaldehyde and YAG-laser capsulotomy in the rabbit
AUTHOR(S): Krootila, Kari; Oksalak, Olli; Von Dickhoff, Kai; Palkama, Arto; Uusitalo, Hannu
CORPORATE SOURCE: Inst. of Biomedicine, Univ. of Helsinki, Helsinki, Finland
SOURCE: Journal of Ocular Pharmacology and Therapeutics (1995), 11(3), 243-52
CODEN: JOPTFU; ISSN: 1080-7683
PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Angiotensin** converting enzyme (ACE)-**inhibitors** **inhibit** degradation of inflammatory mediators substance P (SP) and bradykinin, which may further stimulate the synthesis of prostaglandins. The resulting **increase** in inflammatory mediators in tissue is suggested to be the reason for the dry cough, involving sensory C-fiber activation, among patients receiving ACE-**inhibitor** therapy. In the present study, the effect of an ACE-**inhibitor**, **captopril**, on ocular irritative responses was studied in the rabbit. I.v. **captopril** decreased markedly the blood pressure and modestly the intraocular pressure (IOP). Topical neutral formaldehyde elicits an irritative response in the **eye** mediated through

sensory neuropeptides SP and calcitonin gene-related peptide (CGRP). Following topical neutral formaldehyde, the **increase** in IOP and breakdown of the blood-aqueous barrier were **inhibited** by **captopril**, while miosis was not affected. cAMP content in the aqueous humor was **increased** by **captopril**, and this **increase** was **inhibited** by indomethacin. Following YAG-laser anterior capsulotomy, **captopril inhibited** the **increase** in IOP, breakdown of the blood-aqueous barrier and miosis. The present study demonstrates that use of short-term administration of **captopril** prior to sensory nerve stimulation or YAG laser anterior capsulotomy does not **enhance** the ocular responses to these stimuli in the rabbit. In the present study, **captopril inhibited** these responses, at least partly by decreasing the blood pressure.

L18 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:453050 HCAPLUS
DOCUMENT NUMBER: 113:53050
TITLE: Focal metabolic effects of **angiotensin** and **captopril** on subregions of the rat subfornical organ
AUTHOR(S): Shaver, Steven W.; Kadekaro, Massako; Gross, Paul M.
CORPORATE SOURCE: Dep. Surg., Queen's Univ., Kingston, ON, Can.
SOURCE: Peptides (New York, NY, United States) (1990), 11(3), 557-63
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Angiotensin** infusion **increased** glucose metabolism in 4 of 7 **subdivisions** of the rat subfornical organ, the effect being stronger in ventromedial than in dorsolateral zones across the rostrocaudal axis. [Sar1-Leu8]**Angiotensin** II attenuated metabolic responses to i.v. **angiotensin** in all subfornical organ subregions. Brattleboro rats, having high circulating levels of **angiotensin**, displayed greater rates of glucose metabolism than did Long-Evans rats in all subregions, differences that were eliminated by **captopril**, an **inhibitor** of **angiotensin** -converting enzyme. The studies reveal focal subfornical organ zones where in vivo metabolic activity corresponds to cytoarchitectonic evidence for topog. processing within this **angiotensin**-sensitive structure.

L18 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:453004 HCAPLUS
DOCUMENT NUMBER: 113:53004
TITLE: Prostaglandins mediate the ocular hypotensive action of the **angiotensin** converting enzyme **inhibitor** MK-422 (**enalaprilat**) in African green monkeys
AUTHOR(S): Lotti, Victor J.; Pawlowski, Nancy
CORPORATE SOURCE: Dep. New Lead Pharmacol., Merck Sharp and Dohme Res. Lab., West Point, PA, USA
SOURCE: Journal of Ocular Pharmacology (1990), 6(1), 1-7
CODEN: JOPHER; ISSN: 8756-3320
DOCUMENT TYPE: Journal
LANGUAGE: English
AB MK-422 (**enalaprilat**) (0.005-0.5%) reduced intraocular pressure (IOP) in African Green monkeys. Studies utilizing unilateral instillation of MK-422 and its inactive R-isomer indicated a local site of action within the **eye** which is dependent upon **inhibition** of

angiotensin-converting enzyme (kininase II). Tonog. showed a small **increase** (21%) in conventional aqueous humor outflow facility which did not entirely account for the IOP lowering effect of MK-422. Pretreatment with indomethacin or pilocarpine specifically attenuated the ability of MK-422 to lower IOP, suggesting that biosynthesis of prostaglandins and uveoscleral outflow pathways are important in mediating the ocular hypotension. The data indicate that MK-422 may lower IOP in monkeys by virtue of its ability to prevent the breakdown of bradykinin and thereby promote the formation of endogenous prostaglandins in the **eye**.

L18 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:111808 HCAPLUS
DOCUMENT NUMBER: 112:111808
TITLE: Simultaneous perfusion of rat isolated superior mesenteric arterial and venous beds: comparison of their vasoconstrictor and vasodilator responses to agonists
AUTHOR(S): Warner, Timothy D.
CORPORATE SOURCE: Med. Coll., St. Bartholomew's Hosp., London, EC1M 6BQ, UK
SOURCE: British Journal of Pharmacology (1990), 99(2), 427-33
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A preparation is described that allows a direct comparison of the responses of the perfused arterial and retrogradely perfused venous circulations of the isolated rat superior mesenteric vascular bed. Comparing the responses of the intact arterially perfused mesentery and small intestine to those of the same preparation following removal of the intestine and **division** of the circulations, the **increases** in perfusion pressure produced by arginine-vasopressin (30 pmol) and noradrenaline (1 nmol) were retained by the arterial circulation and those induced by **angiotensin** II (30 pmol) by the venous circulation. Endothelin-1 (30 pmol) constricted both portions of the vasculature but the prolonged nature of its response was associated with only the venous vessels. In the simultaneously perfused arterial and venous preparation arginine vasopressin (3-100 pmol) was a selective constrictor of the arterial circulation and **angiotensin** II (3-100 pmol) of the venous circulation. Noradrenaline (0.3-10 nmol), 5-hydroxytryptamine (0.3-10 nmol), and KCl (1-60 μmol) were more active as constrictors of the arterial than the venous vessels, and U46619 (10-300 pmol) a more active constrictor of the venous than the arterial vessels. Endothelin-1 (3-100 pmol) constricted both the arterial and venous portions of the vasculature but was longer-acting as a venoconstrictor than an arterioconstrictor. **Angiotensin** I (300 pmol) caused constrictions of the venous circulation which were dependent on the presence of **angiotensin** converting enzyme for **captopril** (10 μM) abolished constrictions caused by **angiotensin** I but not by **angiotensin** II. In prepns. preconstricted by U46619 (0.3-3 μM), acetylcholine (0.01-100 nmol), bradykinin (0.001-1 nmol), sodium nitroprusside (0.01-10 nmol) or isoprenaline (1-100 pmol) produced dose-related dilatations of both the arterial and the venous vasculatures, whereas ADP (ADP, 0.01-100 nmol) caused dose-dependent dilatations of the arterial circulation but principally constrictions of the venous circulation. The dilatations caused by acetylcholine and bradykinin in both portions of the circulation, and by ADP in the arterial circulation, were endothelium-dependent as they were **inhibited** by gossypol (3 μM), whereas dilatations to sodium nitroprusside were not. This preparation allows the responses of the arteries and veins of a single perfused

mesenteric bed to be compared. It is possible to demonstrate that veins, as well as arteries, show endothelium-dependent relaxations. The venous portion of the vasculature is involved in the responses of the intact circulation.

L18 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:452572 HCAPLUS
DOCUMENT NUMBER: 109:52572
TITLE: The cardiovascular responses to sequential **inhibition** of alpha-adrenoceptors, the renin-**angiotensin** system and vasopressin in rats with adrenal regeneration hypertension
AUTHOR(S): Foulkes, Roland; Gardiner, Sheila M.; Bennett, Terence
CORPORATE SOURCE: Dep. Physiol. Pharmacol., Queen's Med. Cent., Nottingham, UK
SOURCE: Journal of Hypertension (1988), 6(4), 305-10
CODEN: JOHYD3; ISSN: 0263-6352
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cardiovascular responses to selective α1- and α2-adrenoceptor blockade (with prazosin and idazoxan, resp.) were assessed in rats 4 wks after unilateral nephro-adrenalectomy, contralateral adrenal enucleation, and the **provision** of 1% NaCl in drinking water (AEN rats) and in sham-operated (SON) rats. Measurements were made between 0700 and 1000 h and between 1400 and 1700 h, since resting blood pressures (BP) in AEN rats are higher in the morning than in the afternoon. Following prazosin administration (morning or afternoon), BP fell to similar levels in both SON and AEN rats. Idazoxan, given 20 min after the start of prazosin infusion, caused similar transient falls in BP in all rats. Following the subsequent addnl. **inhibition** of **angiotensin** II (Ang II) production (with **captopril**) and vasopressin (V1) receptors blockade [with d(CH2)5DAVP], BP in AEN rats studied in the morning was higher than in SON rats at that time of day, and higher than in AEN rats studied in the afternoon. There is an addnl. underlying mechanism capable of **increasing** BP in AEN rats studied in the morning.

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=> d que stat l20
L4             1 SEA FILE=REGISTRY ABB=ON  RAMIPRIL/CN
L5             1 SEA FILE=REGISTRY ABB=ON  RAMIPRILAT/CN
L6             1 SEA FILE=REGISTRY ABB=ON  CAPTOPRIL/CN
L7             1 SEA FILE=REGISTRY ABB=ON  ENALAPRILAT/CN
L8             1 SEA FILE=REGISTRY ABB=ON  ANGIOTENSIN I/CN
L9             1 SEA FILE=REGISTRY ABB=ON  ANGIOTENSIN II/CN
L14         8466 SEA FILE=HCAPLUS ABB=ON  (L4 OR L5 OR L6 OR L7 OR ?RAMIPRIL?
                 OR ?RAMIPRILAT? OR ?CAPTOPRIL? OR ?ENALAPRILAT?)
L15         5487 SEA FILE=HCAPLUS ABB=ON  L14 AND (L8 OR L9 OR ?ANGIOTENS?)
L16           10 SEA FILE=HCAPLUS ABB=ON  L15 AND (?VISION? OR ?VISUAL?(W)?ACUIT
                 Y? OR EYE?)(L)(?IMPROV? OR ?ENHANC? OR ?INCREAS?)
L17           10 SEA FILE=HCAPLUS ABB=ON  L16 AND ?INHIBIT?
L19           59 SEA L17
L20           37 DUP REMOV L19 (22 DUPLICATES REMOVED)

=> d ibib abs l20 1-37

L20  ANSWER 1 OF 37  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:   2004120871  EMBASE
TITLE:              Evaluation of Angiotensin-Converting Enzyme
                    Inhibitor Use in Patients with Type 2 Diabetes in a
                    State Managed Care Plan.
AUTHOR:             Timpe E.M.; Amarshi N.; Reed P.J.
CORPORATE SOURCE:   Dr. E.M. Timpe, University of Tennessee, Drug Information
                    Center, 875 Monroe Ave, Memphis, TN 38163, United States.
                    etimpe@utmem.edu
SOURCE:             American Journal of Managed Care, (2004) 10/2 II (124-129).
                    Refs: 16
                    ISSN: 1088-0224  CODEN: AJMCFY
COUNTRY:            United States
DOCUMENT TYPE:      Journal; General Review
FILE SEGMENT:       003     Endocrinology
                    006     Internal Medicine
                    036     Health Policy, Economics and Management
                    037     Drug Literature Index
LANGUAGE:           English
SUMMARY LANGUAGE:   English
AB   Objective: To compare angiotensin-converting enzyme (ACE)
     inhibitor use in patients with type 2 diabetes at 1 year and 3
     years after guidelines were published. Study Design: Retrospective
     database review. Patients and Methods: The drug utilization review
     database of a state managed care plan was accessed to retrieve 2 random
     samples of 500 patients each. These patients had an International
     Classification of Diseases, Ninth Revision, Clinical
     Modification code for diabetes mellitus (250) and a National Drug Code for
     an oral hypoglycemic agent in both 1998 and 2000. Specific clinical
     modification codes, prescription claims, and diagnostic codes were
     obtained from patient profiles. Use of ACE inhibitors in 1998
     and 2000 then was evaluated by using Pearson's chi-square test. Results:
     The proportion of patients with diabetes and hypertension who were taking
     an ACE inhibitor increased by 10 percentage points
     over the 2 years; however, ACE inhibitors were only used in 46%
     of those patients in 2000. A few of the patients receiving an ACE
     inhibitor had a contraindication to use of the agent.
     Microalbuminuria screening and glycosylated hemoglobin screening were
     found to have been conducted in only 4. 6% and 54.6%, respectively, of the
     496 patients in 2000. Conclusions: The results of this study indicate that
     although ACE inhibitor use improved, fewer than 50% of
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patients received appropriate therapy. Awareness of and adherence to the recommendations in the guidelines need to be **improved**. Larger studies may be beneficial to determine more clearly the extent of this problem.

L20 ANSWER 2 OF 37 EMBASE
on STN
ACCESSION NUMBER: 2003464475 EMBASE
TITLE: In-Hospital Initiation of Cardiovascular Protective Medications for Patients Undergoing Percutaneous Coronary Intervention: Taking Advantage of the Teachable Moment.
AUTHOR: Fonarow G.C.
CORPORATE SOURCE: Dr. G.C. Fonarow, UCLA Preventative Cardiology Program, UCLA Division of Cardiology, 47-123 CHS, 10833 Le Conte Avenue, Los Angeles, CA 90095-1679, United States. gfonarow@mednet.ucla.edu
SOURCE: Journal of Invasive Cardiology, (2003) 15/11 (646-652). Refs: 38
ISSN: 1042-3931 CODEN: JOCAFA
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
014 Radiology
017 Public Health, Social Medicine and Epidemiology
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Following percutaneous coronary interventions (PCI), patients remain at risk for atherosclerotic vascular disease progression, cardiovascular events and mortality. There is compelling scientific evidence that antiplatelet therapy, beta-blockers, **angiotensin**-converting enzyme (ACE) **inhibitors** and lipid-lowering therapy reduce cardiovascular events, hospitalizations and mortality in patients after PCI. Despite this evidence and national guidelines, a number of studies in a variety of clinical settings have documented that a significant proportion of post-PCI patients are not receiving treatment with these guideline-recommended, evidence-based therapies when guided by conventional care. The demonstration that initiation of cardiovascular protective medications, including lipid-lowering therapy, prior to hospital discharge for cardiovascular events and/or procedures results in a marked **increase** in treatment rates, **improved** long-term patient compliance and better clinical outcomes has led to the **revision** of national guidelines to endorse this approach as the standard of care. Hospital-based cardiovascular performance **improvement** programs have demonstrated substantial **improvements** in treatment rates as well as the quality of PCI and other coronary heart disease patient care. Adopting in-hospital initiation of cardiovascular protective medications as the standard of care for patients undergoing PCI could dramatically **improve** treatment rates and thus substantially reduce the risk of future cardiovascular events, reduce hospitalizations and prolong life in the large number of patients undergoing PCI each year.

L20 ANSWER 3 OF 37 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004035014 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 14733716
TITLE: **Angiotensin** converting anzyme (ACE) activity in porcine ocular tissue: effects of diet and ACE **inhibitors**.

AUTHOR: Geng Lijun; Persson Karin; Nilsson Siv F E
CORPORATE SOURCE: Department of Medicine and Care, Division of Pharmacology, Faculty of Health Science, Linkoping Universitet, Linkoping, Sweden.
SOURCE: Journal of ocular pharmacology and therapeutics : official journal of the Association for Ocular Pharmacology and Therapeutics, (2003 Dec) 19 (6) 589-98.
Journal code: 9511091. ISSN: 1080-7683.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040122
Last Updated on STN: 20040124

AB The aim of the present experiments was to determine **angiotensin** converting enzyme (ACE) activity in different parts of the porcine **eye**, and to examine whether an atherogenic diet influenced ACE activity. Female mini-pigs were fed a standard diet or a diet with high cholesterol to produce atherosclerosis. The animals were killed by an overdose of pentobarbital, and the **eyes** were enucleated and dissected into iris, ciliary body, retina, and choroid. Crude tissue homogenates were used for determination of ACE activity, which was done with a radioenzymatic assay. In pigs fed a normal diet, basal ACE activity was 18.1 +/- 1.6, 13.6 +/- 1.9, 4.4 +/- 0.6, and 44.7 +/- 8.5 units/mg for iris, ciliary body, retina, and choroid, respectively. The ACE activities in ocular tissues from the pigs that had been fed an atherogenic diet were not significantly different. Nor was the ACE activity in the abdominal aorta and serum significantly different between the two groups. In both groups, the ACE **inhibitors** **captopril** and **enalaprilat**, caused a significant **inhibition** of the ACE activity in the choroid and ciliary body, with **enalaprilat** being more potent. In the retina, ACE activity was **inhibited** significantly only in the group fed a normal diet, whereas ACE activity in the iris was not significantly **inhibited** in either group. We did not find any differences in ACE activity between pigs fed a normal diet and pigs fed an atherogenic diet, which is in disagreement with previous studies that showed an **increased** ACE activity in aorta from atherosclerotic mini-pigs. The reason for this discrepancy is not clear, but lower cholesterol levels are one possibility.

L20 ANSWER 4 OF 37 EMBASE
on STN
ACCESSION NUMBER: 2003391792 EMBASE
TITLE: Radiation nephropathy.
AUTHOR: Cohen E.P.; Robbins M.E.C.
CORPORATE SOURCE: Dr. M.E.C. Robbins, Section Head of Radiation Biology, Department of Radiation Oncology, Wake Forest Univ. School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, United States. mrobbins@wfubmc.edu
SOURCE: Seminars in Nephrology, (2003) 23/5 (486-499).
Refs: 111
ISSN: 0270-9295 CODEN: SNEPDJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
014 Radiology
016 Cancer
028 Urology and Nephrology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
AB The pronounced radiosensitivity of renal tissue limits the total radiotherapeutic dose that can be applied safely to treatment volumes that include the kidneys. The incidence of clinical radiation nephropathy has **increased** with the use of total-body irradiation (TBI) in preparation for bone marrow transplantation and as a consequence of radionuclide therapies. The clinical presentation is azotemia, hypertension, and, disproportionately, severe anemia seen several months to years after irradiation that, if untreated, leads to renal failure. Structural features include mesangiolysis, sclerosis, tubular atrophy, and tubulointerstitial scarring. Similar changes are seen in a variety of experimental animal models. The classic view of radiation nephropathy being inevitable, progressive, and untreatable because of DNA damage-mediated cell loss at **division** has been replaced by a new paradigm in which radiation-induced injury involves not only direct cell kill but also involves complex and dynamic interactions between glomerular, tubular, and interstitial cells. These serve both as autocrine and as paracrine, if not endocrine, targets of biologic mediators that mediate nephron injury and repair. The renin **angiotensin** system (RAS) clearly is involved; multiple experimental studies have shown that antagonism of the RAS is beneficial, even when not initiated until weeks after irradiation. Recent findings suggest a similar benefit in clinical radiation nephropathy.

L20 ANSWER 5 OF 37 EMBASE
on STN
ACCESSION NUMBER: 2003297700 EMBASE
TITLE: Diabetes and hypertension - Double trouble.
AUTHOR: Phillips P.J.; Popplewell P.; Wing L.
CORPORATE SOURCE: Dr. P.J. Phillips, Endocrinology Unit, North Western Adelaide Hlth. Service, The Queen Elizabeth Hospital, Woodville, SA, Australia
SOURCE: Medicine Today, (1 Jul 2003) 4/7 (32-45).
ISSN: 1443-430X CODEN: MTNBCV
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB • Approximately 70% of Australians with type 2 diabetes have the 'double trouble' of diabetes and hypertension. In 75% of these patients, hypertension is untreated or uncontrolled. • Type 2 diabetes is associated with the same coronary risk as having had a myocardial infarct as well as **increased** risks of renal and **eye** damage.
• Studies have shown decreasing cardiovascular risk with decreasing blood pressure and that certain hypotensive agents have advantages in particular situations. • Treating to target (under 130/85 mmHg) and a step approach optimises patient outcomes. • Diabetes management is now directed to the ABCss of diabetes care: control of HbA1c, Blood pressure and Cholesterol, quitting Smoking and using Salicylates.

L20 ANSWER 6 OF 37 EMBASE
on STN
ACCESSION NUMBER: 2002297063 EMBASE

TITLE: The 2001 Canadian recommendations for the management of hypertension: Part two - Therapy.

AUTHOR: McAlister F.A.; Zarnke K.B.; Campbell N.R.C.; Feldman R.D.; Levine M.; Mahon J.; Grover S.A.; Lewanczuk R.; Leenen F.; Tobe S.; Lebel M.; Stone J.; Schiffrin E.L.; Rabkin S.W.; Ogilvie R.I.; Larochelle P.; Jones C.; Honos G.; Fodor G.; Burgess E.; Hamet P.; Herman R.; Irvine J.; Culleton B.; Wright J.M.

CORPORATE SOURCE: Dr. F.A. McAlister, 2E3.24 WMC, University of Alberta Hospital, 8440 112 Street, Edmonton, Alta. T6G 2R7, Canada. Finlay.McAlister@ualberta.ca

SOURCE: Canadian Journal of Cardiology, (2002) 18/6 (625-641).
Refs: 75
ISSN: 0828-282X CODEN: CJCAEX

COUNTRY: Canada
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
036 Health Policy, Economics and Management
038 Adverse Reactions Titles
030 Pharmacology
003 Endocrinology
028 Urology and Nephrology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; French

AB Objective: To provide updated, evidence-based recommendations for the therapy of hypertension in adults. Options: For patients with hypertension, a number of antihypertensive agents may control blood pressure. Randomized trials evaluating first-line therapy with thiazides, beta-adrenergic antagonists, **angiotensin**-converting enzyme **inhibitors**, calcium channel blockers, alpha-blockers, centrally acting agents or **angiotensin** II receptor antagonists were reviewed. Outcomes: The health outcomes that were considered were changes in blood pressure, cardiovascular morbidity, and cardiovascular and/or all-cause mortality rates. Economic outcomes were not considered due to insufficient evidence. Evidence: MEDLINE was searched for the period March 1999 to October 2001 to identify studies not included in the 2000 **revision** of the Canadian Recommendations for the Management of Hypertension. Reference lists were scanned, experts were polled, and the personal files of the subgroup members and authors were used to identify other published studies. All relevant articles were reviewed and appraised, using prespecified levels of evidence, by content experts and methodological experts. Values: A high value was placed on the avoidance of cardiovascular morbidity and mortality. Benefits, harms and costs: Various antihypertensive agents reduce the blood pressure of patients with sustained hypertension. In certain settings, and for specific classes of drugs, blood-pressure lowering has been associated with reduced cardiovascular morbidity and/or mortality. Recommendations: The present document contains detailed recommendations pertaining to treatment thresholds, target blood pressures, and choice of agents in various settings in patients with hypertension. The main changes from the 2000 Recommendations are the addition of a section on the treatment of hypertension in patients with diabetes mellitus, the amalgamation of the previous sections on treatment of hypertension in the young and old into one section, **increased** emphasis on the role of combination therapies over repeated trials of single agents and expansion of the section on the treatment of hypertension after stroke. Implicit in the recommendations for therapy is the principle that treatment for an individual patient should take into consideration global cardiovascular

risk, the presence and/or absence of target organ damage, and comorbidities. Validation: All recommendations were graded according to strength of the evidence and voted on by the Canadian Hypertension Recommendations Working Group. Individuals with potential conflicts of interest to any specific recommendation were excluded from voting on that recomendation. Only those recommendations achieving high levels of consensus are reported here. These guidelines will continue to be updated annually.

L20 ANSWER 7 OF 37 EMBASE
on STN

ACCESSION NUMBER: 2002297062 EMBASE
TITLE: The 2001 Canadian recommendations for the management of hypertension: Part one - Assessment for diagnosis, cardiovascular risk, causes and lifestyle modification.
AUTHOR: Zarnke K.B.; McAlister F.A.; Campbell N.R.C.; Levine M.; Schiffrin E.L.; Grover S.; McKay D.W.; Myers M.G.; Wilson T.W.; Rabkin S.W.; Feldman R.D.; Burgess E.; Bolli P.; Honos G.; Lebel M.; Mann K.; Abbott C.; Tobe S.; Petrella R.; Touyz R.M.
CORPORATE SOURCE: Dr. K.B. Zarnke, London Health Sciences Centre, University Hospital Campus, 339 Windermere Road, London, Ont. N6A 5A5, Canada. Kelly.Zarnke@lhsc.on.ca
SOURCE: Canadian Journal of Cardiology, (2002) 18/6 (604-624).
Refs: 185
ISSN: 0828-282X CODEN: CJCAEX
COUNTRY: Canada
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
030 Pharmacology
038 Adverse Reactions Titles
029 Clinical Biochemistry
036 Health Policy, Economics and Management
003 Endocrinology
028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; French

AB Objective: To provide updated, evidence-based recommendations for the assessment of the diagnosis, cardiovascular risk, identifiable causes and lifestyle modifications for adults with high blood pressure. Options: For persons in whom a high blood pressure value is recorded, hypertension is diagnosed based on the appropriate measurement of blood pressure, the level of the blood pressure elevation and the duration of follow-up. In addition, the presence of concomitant vascular risk factors, target organ damage and established atherosclerotic diseases must be assessed to determine the urgency, intensity and type of treatment. For persons receiving a diagnosis of hypertension, defining the overall risk of adverse cardiovascular outcomes requires an assessment of concomitant vascular risk factors, including laboratory testing, a search for target organ damage and an assessment for modifiable causes of hypertension. Home and ambulatory blood pressure assessment and echocardiography are options for selected patients. Outcomes: The outcomes were: the identification of persons at **increased** risk of adverse cardiovascular outcomes; the quantification of overall cardiovascular risk; and the identification of persons with potentially modifiable causes of hypertension. Evidence: MEDLINE searches were conducted from one year before the period of the last **revision** of the Canadian recommendations for the management of hypertension (May 1999 to May 2001). Reference lists were scanned, experts were polled, and the personal files of the subgroup members and

authors were used to identify other studies. Identified articles were reviewed and appraised, using prespecified levels of evidence, by content experts and methodological experts. In addition to an update of the previous year's review, new sections on assessing overall cardiovascular risk and endocrine causes are provided. Values: A high value was placed on the identification of persons at **increased** risk of cardiovascular morbidity and mortality, and of persons with identifiable causes of hypertension. Benefits, harms and costs: The identification of persons at higher risk of cardiovascular disease will permit counseling for lifestyle manoeuvres and introduction of antihypertensive drugs to reduce blood pressure for patients with sustained hypertension. The identification of specific causes of hypertension may permit the use of cause-specific interventions. In certain subgroups of patients, and for specific classes of drugs, blood pressure lowering has been associated with reduced cardiovascular morbidity or mortality. Recommendations: The present document contains recommendations for the assessment of the diagnosis, cardiovascular risk, identifiable causes and lifestyle modifications for adults with high blood pressure. These include the accurate measurement of blood pressure, criteria for the diagnosis of hypertension and recommendations for follow-up, assessment of overall cardiovascular risk, routine and optional laboratory testing, assessment for renovascular and endocrine causes, home and ambulatory blood pressure monitoring, the role of endocardiography and lifestyle modifications. Validation: All recommendations were graded according to the strength of the evidence and voted on by the Canadian Hypertension Recommendations Working Group. Only those recommendations achieving high levels of consensus are reported. These guidelines will be updated annually. Endorsement: These guidelines are endorsed by the Canadian Hypertension Society, The Canadian Coalition for High Blood Pressure and Control, The College of Family Physicians of Canada, The Heart and Stroke Foundation of Canada, The Adult Disease **Division** and Bureau of Cardio-Respiratory Diseases and Diabetes at the Centre for Chronic Disease Prevention and Control, Health Canada.

L20 ANSWER 8 OF 37 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002272114 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12011739
TITLE: [Experience with **Ramipril** (Triatec(R)) in the treatment of glaucomatous neuropathy].
Traitement de la neuropathie glaucomateuse par le **Ramipril** (Triatec(R)).
AUTHOR: Rekik R
CORPORATE SOURCE: 3 avenue Louis Braille, 1002 Tunis (Tunisie), France.
SOURCE: Journal francais d'ophtalmologie, (2002 Apr) 25 (4) 357-65.
Journal code: 7804128. ISSN: 0181-5512.
PUB. COUNTRY: France
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20020726
Entered Medline: 20020725

AB PURPOSE: The main purpose of this study was to assess the **improvement** in visual function in patients with glaucomatous neuropathy treated with **Ramipril** (**angiotensin**-converting enzyme **inhibitor**); we were thus able to link ischemia and visual deterioration in glaucoma. **Ramipril** **increases** endothelium-dependent relaxation and vasodilatation to

bradykinin via B2 receptors linked to the formation of nitric oxide (NO). On the other hand, **Ramipril** could have an influence on retinal neurotransmission modulation. Materials and methods: **Ramipril** was administered to 22 patients suffering from chronic glaucoma in whom intraocular pressure (IOP) was controlled by classic treatment, combining **Ramipril** with this treatment. It was given orally (1.25mg daily) for 3 months in order to **improve** visual function. In addition to the standard follow-up (**visual acuity**, intraocular pressure, automatic perimetry, optic disk), this study focused on the systemic tolerance to **Ramipril**. RESULTS: Thirty **eyes** in 22 patients were evaluated. Mean intraocular pressure did not change, but the mean **visual acuity improved** from 0.53 to 0.74. After 3 months of treatment, the perimetric test (Octopus) showed an **improvement** in the mean defect (MD) (48%) and the corrected loss variance (CLV) (54%). No complications in terms of arterial pressure were observed. CONCLUSION: This study has shown that **Ramipril** was an effective agent in glaucomatous neuropathy. It **improved** visual function without changing IOP and had a satisfactory general tolerance in all patients. This could be explained in part by a higher production of NO by endothelial cells. This gas is a powerful vasodilator. It is formed from L-arginine by constitutive nitric oxide synthetase. This would provide an **improvement** in local blood flow autoregulation altered in glaucoma by an endothelial dysfunction.

L20 ANSWER 9 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001372835 EMBASE
TITLE: The impact of specialists on prescribing by general practitioners.
AUTHOR: Robertson J.; Fryer J.L.; O'Connell D.L.; Sprogis A.; Henry D.A.
CORPORATE SOURCE: Prof. D.A. Henry, School of Population Health Sciences, Fac. of Med. and Health Sciences, University of Newcastle, Newcastle, NSW, Australia. mddah@mail.newcastle.edu.au
SOURCE: Medical Journal of Australia, (15 Oct 2001) 175/8 (407-411).
Refs: 26
ISSN: 0025-729X CODEN: MJAUAJ
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective: To investigate the direct impact of specialists on prescribing by general practitioners. Design: Cross-sectional, prescription-based study. Subjects and setting: 88 GPs in the Hunter Urban **Division** of General Practice, Hunter Valley, NSW. Main outcome measure: Proportions of specialist-initiated prescriptions for eight commonly prescribed drug classes. Results: The proportion of specialist-initiated prescriptions was greatest for proton pump **inhibitors** (85%), and lowest for diuretics (8%), newer antidepressants (10%) and H(2)-receptor antagonists (13%). Specialists initiated 29% of prescriptions for β-blockers, 26% for calcium-channel blockers, 20% for statins and 19% for **angiotensin**-converting enzyme **inhibitors** or **angiotensin** II antagonists. Specialists were more likely to have been involved in starting therapy with metoprolol than other β-blockers (51% v 23%) and diltiazem than other calcium-channel

blockers (48% v 19%), and this was related to indication for treatment. In contrast, prescriptions for the more recently introduced drugs (**angiotensin** II antagonists and atorvastatin) were not more likely to have been specialist-initiated than prescriptions for established **angiotensin**-converting enzyme **inhibitors** and statins. Conclusions: The direct impact of specialists on prescribing in the Hunter Urban **Division** of General Practice is substantial and varies with the drug class. This highlights the need to engage both GPs and specialists in efforts to **improve** prescribing practices.

L20 ANSWER 10 OF 37 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000279361 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10821341
TITLE: Short-term **angiotensin** converting enzyme **inhibition** reduces basal tone and dilator reactivity in skeletal muscle arterioles.
AUTHOR: Frisbee J C; Lombard J H
CORPORATE SOURCE: Department of Physiology, Medical College of Wisconsin, Milwaukee 53226, USA.. jfrisbee@mcw.edu
CONTRACT NUMBER: HL29587 (NHLBI)
HL37374 (NHLBI)
HL52211 (NHLBI)
SOURCE: American journal of hypertension : journal of the American Society of Hypertension, (2000 Apr) 13 (4 Pt 1) 389-95. Journal code: 8803676. ISSN: 0895-7061.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000727
AB Alterations in resting tone, maximum diameter, and dilator reactivity to acetylcholine (ACH) and sodium nitroprusside (SNP) were assessed in cremaster muscle microvessels of Sprague-Dawley rats receiving **angiotensin** converting enzyme (ACE) **inhibition** with **captopril** for 4 days and in untreated time-control rats. The transilluminated in situ cremaster muscle was superfused with physiologic salt solution (PSS) and viewed via **television** microscopy; arteriolar diameter was measured using a videomicrometer. Before agonist challenge, resting arteriolar diameter was significantly **increased** in **captopril**-treated rats. Although maximum arteriolar diameter (determined during superfusion of the cremaster muscle with Ca2+-free PSS containing 10(-4) mol/L adenosine) was not altered with ACE **inhibition**, the maximum possible arteriolar dilation was reduced in **captopril**-treated rats. **Captopril** administration reduced both ACH- and SNP-induced dilation of cremasteric arterioles compared with responses in control rats, although this was partially a function of the reduced capacity for dilation, primarily to SNP. These observations indicate that short-term ACE **inhibition** reduces both resting tone and agonist-induced dilator responses of skeletal muscle arterioles.

L20 ANSWER 11 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000436553 EMBASE
TITLE: Perioperative treatment of congestive heart failure.
AUTHOR: Clark L.L.
CORPORATE SOURCE: Dr. L.L. Clark, Anesthesiology Department, University

Hospital, 530 S Jackson St, Louisville, KY 40202, United States
SOURCE: Seminars in Cardiothoracic and Vascular Anesthesia, (2000) 4/4 (223-235).
Refs: 69
ISSN: 1089-2532 CODEN: SCVAFI
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
024 Anesthesiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Congestive heart failure is a common disease that affects 5 million people and will continue to **increase** in prevalence as the population ages. Estimates of its prevalence in patients presenting for vascular surgery range up to 50%. It has been consistently shown to be associated with **increased** mortality after vascular surgery. The anesthesiologist's contact with this disease entity will **increase** as well. Little has changed in the treatment of this disease until recently. Many new developments have occurred in the pathophysiology and the treatment of this age-old disease. This article reviews developments in the pathophysiology, which have resulted in a new understanding and a complete **revision** of the recommendations for the treatment of hear failure as well as some modalities that hold promise for the future.

L20 ANSWER 12 OF 37 EMBASE
on STN
ACCESSION NUMBER: 2000119304 EMBASE
TITLE: Optimising delivery of care for chronic heart failure.
AUTHOR: Clark A.L.; Cleland J.G.F.
CORPORATE SOURCE: Dr. A.L. Clark, Department of Cardiology, Castle Hill Hospital, Castle Road, Cottingham, Hull HU16 5JQ, United Kingdom. A.L.Clark@Medschool.hull.ac.uk
SOURCE: Journal of Clinical Excellence, (2000) 1/4 (209-215).
Refs: 44
ISSN: 1465-9883 CODEN: JCEXF5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The management of chronic heart failure is becoming **increasingly** complex. Large clinical trials have demonstrated that the prognosis of heart failure can be modified by treatment, with beneficial effects on patients' symptoms and hospitalisation rates. The diagnosis of heart failure is the cornerstone of good management, and at present is largely dependent on the **provision** of echocardiography services. Heart failure treatment should now consist of a diuretic for relief of fluid retention and an **angiotensin**-converting enzyme **inhibitor** . In addition, it is now clear that a β-adrenergic receptor antagonist is an essential component of management, but that this requires specialist management. Spironolactone has also been shown to confer a mortality benefit in some patient groups. These layers of complexity suggest that the **provision** of a clinical heart failure service is important. The trial evidence that exists suggests that where patients are managed by heart failure specialists, they are more likely to be on

appropriate treatment, and to have lower hospital admission rates. A central role can be played by dedicated specialist nurses in helping to manage the patient's illness in the community. We discuss the evidence in favour of a specialist service **provision** and describe how such a specialist heart failure service might be structured and run.

L20 ANSWER 13 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000412913 EMBASE
TITLE: An audit of acute myocardial infarction in a district general hospital: Results and recommendations.
AUTHOR: Owen A.; Husk J.
CORPORATE SOURCE: Dr. A. Owen, Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent CT1 3LP, United Kingdom
SOURCE: Journal of Clinical Excellence, (2000) 2/2 (111-118). Refs: 27
ISSN: 1465-9883 CODEN: JCEXF5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
017 Public Health, Social Medicine and Epidemiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objectives: To audit the treatment of acute myocardial infarction in a district general hospital. Design: Prospective review of case notes of all patients with a myocardial infarction admitted over two 3-month periods, with a 5-month interval for education and the dissemination of results. Setting: A district general hospital. Main outcome measures and results: Data are presented with the findings for the second audit period in parenthesis. There were 86(80) patients. The proportion of patients eligible for thrombolytic therapy who received it was 94(94)%; the proportion who received it appropriately was 88(94)%; median door to needle time was 32(27) min. The proportion of patients receiving aspirin at, or before, admission was 78(92)% ($P < 0.02$), with a median time to administration of 41 (37) min; the proportion prescribed at least the recommended dose at discharge was 2(59)% ($P < 0.001$); the proportion discharged on aspirin was 88(88)%. The proportion of patients prescribed intravenous beta-blockers was 8(5)%, oral beta-blockers was 48(48)%, with a median time to administration of 14(18) h; the proportion of patients discharged on a beta-blocker were 51(60)%. The proportion of patients prescribed **angiotensin** converting enzyme (ACE) **inhibitors** on admission were 47(52)%, with a median time to administration of 42(51) h; the proportion of patients discharged on ACE **inhibitors** was 61 (61)%, and proportion on at least the recommended dose was 47(50)%. Elderly patients were less likely to receive beta-blockers ($P < 0.001$) or ACE **inhibitor** therapy ($P < 0.05$). Conclusions: The audit process has substantially **improved** the **provision** of aspirin therapy, but not greatly affected the other treatments. The **provision** of thrombolytic, beta-blocker and ACE **inhibitor** therapy appears to be similar to that published in the literature but this leaves room for substantial **improvement**.

L20 ANSWER 14 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000063212 EMBASE
TITLE: Pathoaetiology, epidemiology and diagnosis of hypertension.
AUTHOR: Brown M.J.; Haydock S.
CORPORATE SOURCE: Prof. M.J. Brown, Clinical Pharmacology Unit, University of

Cambridge, Box 110, Cambridge CB2 2QQ, United Kingdom
SOURCE: Drugs, (2000) 59/SUPPL. 2 (1-12).
Refs: 48
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Hypertension is currently defined in terms of levels of blood pressure associated with **increased** cardiovascular risk. A cut-off of 140/90mm Hg is accepted as a threshold level above which treatment should at least be considered. This would give a prevalence of hypertension of about 20% of the adult population in most developed countries. Hypertension is associated with **increased** risk of stroke, myocardial infarction, atrial fibrillation, heart failure, peripheral vascular disease and renal impairment. Hypertension results from the complex interaction of genetic factors and environmental influences. Many of the genetic factors remain to be discovered, but environmental influences such as salt intake, diet and alcohol form the basis of nonpharmacological methods of blood pressure reduction. Investigation of the individual hypertensive patient aims to identify possible secondary causes of hypertension and also to assess the individual's overall cardiovascular risk, which determines the need for prompt and aggressive therapy. Cardiovascular risk can be determined from (i) target organ damage to the **eyes**, heart and kidneys; (ii) other medical conditions associated with **increased** risk; and (iii) lifestyle factors such as obesity and smoking. Secondary causes of hypertension are individually rare. Screening tests should be initially simple, with more expensive and invasive tests reserved for those in whom a secondary cause is suspected or who have atypical features to their presentation. The main determinants of blood pressure are cardiac output and peripheral resistance. The typical haemodynamic finding in patients with established hypertension is of normal cardiac output and **increased** peripheral resistance. Treatment of hypertension should initially use nonpharmacological methods. Selection of initial drug therapy should be based upon the strength of evidence for reduction of cardiovascular mortality in controlled clinical trials, and should also take into account coexisting medical conditions that favour or limit the usefulness of any given drug. Given this approach, it would be reasonable to use a thiazide diuretic and/or a β-blocker as first-line therapy unless there are indications to the contrary. Individual response to given drug classes is highly variable and is related to the underlying variability in the abnormal pathophysiology. There are data to suggest that the renin-**angiotensin** system is more important in young patients. The targeting of this system in patients under the age of 50 years with a β-blocker (or ACE **inhibitor**), and the use of a thiazide diuretic (or calcium antagonist) in patients over 50 years, may enable blood pressure to be controlled more quickly.

L20 ANSWER 15 OF 37 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2000035186 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10564200
TITLE: Central administration of the somatostatin analog octreotide induces **captopril**-insensitive sleep responses.
AUTHOR: Beranek L; Hajdu I; Gardi J; Taishi P; Obal F Jr; Krueger J M

CORPORATE SOURCE: Department of Physiology, A. Szent-Gyorgyi Medical University, 6720 Szeged, Hungary.
CONTRACT NUMBER: NS-25378 (NINDS)
NS-27250 (NINDS)
SOURCE: American journal of physiology, (1999 Nov) 277 (5 Pt 2) R1297-304.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991220

AB The effects of intracerebroventricular injections of the long-lasting somatostatin analog octreotide (Oct) were studied on sleep and behavior in rats. Pyrogen-free physiological saline and Oct (0.001, 0.01, 0.1 microgram) or vehicle were administered at light onset, and the electroencephalogram (EEG), motor activity, and cortical brain temperature were recorded during the 12-h light period. Plasma growth hormone (GH) concentrations were measured in samples taken at 30-min intervals after Oct. Oct (0.01 and 0.1 microgram) suppressed non-rapid **eye** movement sleep (NREMS) for 1-2 h. NREMS intensity (delta EEG activity during NREMS) dose dependently **increased** in hour 3 postinjection and thereafter (0.1 microgram). Plasma GH concentrations were suppressed after Oct (0.01 and 0.1 microgram), but pulses of GH secretions occurred 90-120 min postinjection in each rat. Oct (0.1 microgram) **enhanced** behavioral activity, including prompt drinking followed by grooming, scratching, and feeding. Intracerebroventricular injection of the **angiotensin**-converting enzyme **inhibitor** **captopril** (30 microgram, 10 min before Oct), blocked these behavioral responses but not the Oct-induced sleep alterations. The changes in sleep after intracerebroventricular Oct suggest an intracerebral action site and might result from Oct-induced variations in the sleep-promoting activity of GH-releasing hormone.

L20 ANSWER 16 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999182897 EMBASE
TITLE: Renin-**angiotensin** system, hypertrophy and gene expression in cardiac myocytes.
AUTHOR: Lijnen P.; Petrov V.
CORPORATE SOURCE: Prof. P. Lijnen, Hypertension Unit, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium
SOURCE: Journal of Molecular and Cellular Cardiology, (1999) 31/5 (949-970).
Refs: 49
ISSN: 0022-2828 CODEN: JMCDAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In response to humoral and mechanical stimuli, the myocardium adapts to **increased** work load through hypertrophy of individual muscle

cells. Myocardial hypertrophy is characterized by an **increase** in cell size in the absence of cell **division** and is accompanied by changes in gene expression. **Angiotensin** II (ANGII), the effector peptide of the renin-**angiotensin** system (RAS), regulates volume and electrolyte homeostasis and is involved in cardiac and vascular growth in rats. In this review, the role of RAS on the myocyte protein synthesis (myocyte hypertrophy) and on the induction of gene expression will be discussed in rat cardiomyocytes in culture. The traditional RAS can be considered as a system in which circulating ANGII is delivered to target tissues or cells. However, a local RAS has also been described in cardiac cells and evidence has been accumulated for autocrine and/or paracrine pathways by which biological actions of ANGII can be mediated. These actions of ANGII are primarily mediated through ANGII receptors of the subtype I (AT1-R). When evaluating the effects of ANGII in situ, both changes in circulating levels and local production have to be taken into account. Discrepant findings on the in vitro effect of ANGII on the protein synthesis in cardiac myocytes are described and can be at least partly be attributed to methodological problems such as assay of the de novo protein synthesis, isolation and the separation procedure of cardiac myocytes. The ANGII-induced hypertrophic effect also depends on the existence of non-myocytes in a cardiocyte culture. In rat cardiocytes ANGII also causes induction of many immediately-early genes (c-fos, c-jun, jun-B, Egr-1 and c-myc) and induces also late markers of cardiac hypertrophy (skeletal α-actin and atrial natriuretic peptide expression) and growth factors (TGF-β1 gene expression). In vivo ANGII via AT1-R, causes not only ventricular hypertrophy, independently of blood pressure, but also a shift to the fetal phenotype of the myocardium. **Angiotensin**-converting enzyme **inhibitors** and ANGII receptor antagonists of the subtype I not only induce the regression, but also prevent the development of cardiac hypertrophy in experimental rat models.

L20 ANSWER 17 OF 37 EMBASE
on STN

ACCESSION NUMBER: 1999219778 EMBASE
TITLE: Antagonism of the renin-**angiotensin** system, hypertrophy and gene expression in cardiac myocytes.
AUTHOR: Lijnen P.; Petrov V.
CORPORATE SOURCE: Prof. P. Lijnen, Hypertension Unit, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. paul.lijnen@med.kuleuven.ac.be
SOURCE: Methods and Findings in Experimental and Clinical Pharmacology, (1999) 21/5 (363-374).
Refs: 113
ISSN: 0379-0355 CODEN: MFEPDX
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In response to humoral and mechanical stimuli, the myocardium adapts to **increased** work load through hypertrophy of individual muscle cells. Myocardial hypertrophy is characterized by an **increase** in cell size in the absence of cell **division** and is accompanied by changes in gene expression. **Angiotensin** II (Ang II), the effector peptide of the renin-**angiotensin** system (RAS), regulates volume and electrolyte homeostasis and is involved in cardiac and vascular growth in rats. In this review, the role of RAS in myocyte

protein synthesis (myocyte hypertrophy) and in induction of gene expression will be discussed in rat cardiomyocytes in culture. Traditional RAS can be considered as a system in which circulating Ang II is delivered to target tissues or cells. However, a local RAS has also been described in cardiac cells and evidence has been accumulated for autocrine and/or paracrine pathways by which biological actions of Ang II can be mediated. These actions Ang II are primarily mediated through Ang II receptors subtype I (AT-R). When evaluating the effects Ang II in situ, both changes in circulating levels and local production have to be taken into account. Contrasting results have been found concerning the in vitro effect Ang II on the protein synthesis in cardiac myocytes and can be at least partly be attributed to methodological problems such as assay of de novo protein synthesis and isolation and separation procedure of cardiac myocytes. The Ang II-induced hypertrophic effect also depends on the existence of nonmyocytes in a cardiocyte culture. In rat cardiocytes, AngII also causes induction of many immediately-early genes (c-f os c-jun, jun-B, Egr-I and c-myc and induces also late markers of cardiac hypertrophy (skeletal α-actin and atrial natriuretic peptide expression) and growth factors (TGF-β, gene expression), In vivo AngII via AT1-R, causes not only ventricular hypertrophy but also a shift to the fetal phenotype of the myocardium. **Angiotensin**-converting enzyme **inhibitors** and AngII receptor antagonists of the subtype I not only induce the regression but also prevent the development of cardiac hypertrophy in experimental rat models.

L20 ANSWER 18 OF 37 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1998224031 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9562936
TITLE: Patterns of **angiotensin**-converting enzyme **inhibitor** prescriptions, educational interventions, and outcomes among hospitalized patients with heart failure.
AUTHOR: McDermott M M; Lee P; Mehta S; Gheorghiade M
CORPORATE SOURCE: Division of General Internal Medicine, Northwestern University Medical School, Chicago, Illinois, USA.
SOURCE: Clinical cardiology, (1998 Apr) 21 (4) 261-8.
Journal code: 7903272. ISSN: 0160-9289.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980618
Last Updated on STN: 19980618
Entered Medline: 19980609

AB BACKGROUND: Among hospitalized patients with heart failure, we describe characteristics associated with prescription of **angiotensin** -converting enzyme (ACE) **inhibitors** in the doses recommended by clinical practice guidelines. We also describe the impact of ACE **inhibitor** prescriptions, **increases** in ACE **inhibitor** dose, and nonpharmacologic educational interventions on readmission-free survival rates. HYPOTHESIS: We hypothesize that care by a cardiologist physician and higher mean arterial blood pressure on admission are associated with receipt of optimal ACE **inhibitor** doses. We hypothesize that receipt of an ACE **inhibitor** at discharge and an **increase** in ACE **inhibitor** dose during hospitalization are associated with superior readmission-free survival. METHODS: Between January 1, 1992, and December 31, 1993, medical records were reviewed for consecutively hospitalized patients with a principal diagnosis of heart failure at an academic medical center. Documented

instructions and medications prescribed at discharge were abstracted. Deaths and readmissions through December 31, 1994, were identified with the National Death Index and the study institution's administrative data base, respectively. RESULTS: During 1992 and 1993, 387 patients were discharged alive from hospitalization for heart failure. Among patients discharged on enalapril or **captopril**, 18% received doses recommended by heart failure clinical practice guidelines. Patients discharged on a recommended ACE **inhibitor** dose were more likely to be African-American and had lower sodium levels and higher mean arterial pressures than patients discharged on lower ACE **inhibitor** doses. In survival analyses, an **increase** in ACE **inhibitor** dose was associated with **improved** readmission-free survival, independent of left ventricular systolic function type. Receipt of an ACE **inhibitor** at discharge was also associated with superior readmission-free survival, while nonpharmacologic educational instructions were not associated with **improved** outcomes. CONCLUSION: Interventions are needed to **improve** the frequency with which ACE **inhibitors** are prescribed at recommended doses to hospitalized patients with heart failure. We conclude that among these patients, receipt of an ACE **inhibitor** at discharge and an **increase** in ACE **inhibitor** dose during hospitalization are each associated with measurable effects on readmission-free survival, while **provision** of educational instructions as currently practiced is not associated with better outcomes.

L20 ANSWER 19 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998070268 EMBASE
TITLE: Vascular hypertrophy in hypertension: Role of the renin-**angiotensin** system.
AUTHOR: Rosendorff C.
CORPORATE SOURCE: Dr. C. Rosendorff, Medical Service (111), Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468, United States
SOURCE: Mount Sinai Journal of Medicine, (1998) 65/2 (108-117). Refs: 102
ISSN: 0027-2507 CODEN: MSJMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Angiotensin** II is vasoconstrictor and antinatriuretic; it also stimulates cell growth and proliferation in vascular smooth muscle, resulting in hypertrophy or hyperplasia of conduit and resistance vessels. These actions are mediated through **angiotensin** II receptors (AT1 subtype), which activate several G-protein-dependent intracellular transduction pathways, such as the phospholipase C, diacylglycerol and inositol triphosphate pathways, the mitogen-activated protein (MAP) kinase pathway, and Janus kinase (JAK)-signal transducers and activators of the transcription (STAT)- mediated pathway. These can all **increase** the expression of certain proto- oncogenes, particularly c-fos. **Angiotensin** II also stimulates the activity of certain growth factors, such as platelet-derived growth factor-A-chain and basic fibroblast growth factor. The cellular responses to **angiotensin** II in vascular smooth muscle have been shown in different hypertensive vessels to be either hypertrophy alone, hypertrophy and DNA synthesis

without cell **division** (polyploidy), or DNA synthesis with cell **division** (hyperplasia). In genetic hypertension, there is either cellular hyperplasia or remodeling, whereas in renovascular hypertension, there is hypertrophy of vascular smooth muscle cells. **Angiotensin** -converting enzyme (ACE) **inhibitors** prevent or reverse vascular hypertrophy in animal models of hypertension. In human hypertension, ACE **inhibitors** reduce the **increased** media/lumen ratio of large and small arteries and **increase** arterial compliance. These properties are also shared by AT1 receptor antagonists. The implications of these findings for morbidity and mortality in hypertension still await rigorous testing in prospective clinical trials.

L20 ANSWER 20 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96356034 EMBASE
DOCUMENT NUMBER: 1996356034
TITLE: Changing patterns of investigation and treatment of cardiac failure in hospital.
AUTHOR: Hillis G.S.; Al-Mohammad A.; Wood M.; Jennings K.P.
CORPORATE SOURCE: Department of Medicine/Therapeutics, University of Aberdeen, Medical School,Foresterhill, Aberdeen AB9 2ZD, United Kingdom
SOURCE: Heart, (1996) 76/5 (427-429).
ISSN: 1355-6037 CODEN: HEARFR
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective - To assess the investigation and treatment of cardiac failure in 1995 and to compare this with management in 1992. Design - Retrospective consecutive case study. Setting - University teaching hospital. Subjects - All patients (n = 265) discharged from Aberdeen Royal Infirmary in the first quarter (January 1-31 March) of 1995 with a diagnosis of congestive cardiac failure, left ventricular failure, or heart failure (unspecified). These correspond to the International Classification of Diseases 9th **revision** codings of 428.0, 428.1, and 428.9 respectively. Methods - Sociodemographic and clinical data were extracted from the case notes of the above subjects and compared with similar data from the final six months of 1992. Main outcome measures - The use of echocardiography in confirming the diagnosis and delineating the aetiology of heart failure and the use of **angiotensin** -converting enzyme (ACE) **inhibitors** in the treatment of patients diagnosed as having heart failure and without contraindications to these agents. Results - The number of patients discharged in 1995 with a diagnosis including cardiac failure had **increased** by 55.7% since 1992. The use of echocardiography had also risen from 36.6% to 72% ($P < 0.0001$) with an associated **increase** in the proportion of patients discharged on treatment with an ACE **inhibitor** (40% in 1992 v 55.1% in 1995: $P < 0.001$). The doses of ACE **inhibitors** used had also **increased** significantly ($P < 0.001$). Most patients with cardiac failure continue to be treated by general physicians, who are less likely to use echocardiography ($P < 0.01$) or prescribe an ACE **inhibitor** ($P < 0.05$) than cardiologists. Conclusions - There is **increasing** recognition, more thorough investigation, and **improved** treatment of heart failure. Despite this there are grounds for concern, both in terms of the adequacy of management and

resource implications.

L20 ANSWER 21 OF 37 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 95197358 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7890486
TITLE: Local action of the renin **angiotensin** system in the porcine ophthalmic circulation: effects of ACE-**inhibitors** and **angiotensin** receptor antagonists.
AUTHOR: Meyer P; Flammer J; Luscher T F
CORPORATE SOURCE: Department of Ophthalmology, University Hospital, Basel, Switzerland.
SOURCE: Investigative ophthalmology & visual science, (1995 Mar) 36 (3) 555-62.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950427
Last Updated on STN: 19950427
Entered Medline: 19950417

AB PURPOSE. The renin **angiotensin** system and endothelium-derived substances are important regulators of the microcirculation. The authors studied the roles of **angiotensins** (Ang), **angiotensin** converting enzyme (ACE)-**inhibitors**, and Ang II-receptor antagonists in the porcine ophthalmic circulation. METHODS. Isolated porcine ciliary arteries were studied in myographs and the intact porcine **eye** in a perfusion system at 80 cm H2O perfusion pressure with Krebs-ringer bicarbonate solution (37 degrees C, 95% O2, 5% CO2). RESULTS. ACE-**inhibitors enalaprilat** and benazepril (both 10(-5) M) did not change ciliary vascular tone nor flow of perfused porcine **eyes**. However, **enalaprilat** or benazepril **enhanced** the relaxation of ciliary arteries to bradykinin ($P < 0.02$). In the perfused porcine **eye**, **enalaprilat** (10(-5) M) augmented vasodilation to bradykinin ($P < 0.02$). The bradykinin antagonist Hoe 140 (3 x 10(-7) M) prevented the relaxation of ciliary arteries to bradykinin ($P < 0.001$), but not to acetylcholine. In perfused **eyes**, Hoe 140 reduced the vasodilation to bradykinin ($P < 0.01$). Ang II (10(-8) to 10(-6) M) evoked a contraction of ciliary arteries and was more potent than Ang I. **Enalaprilat** abolished the effect of Ang I. The AT1-receptor antagonist, valsartan (10(-9) to 10(-5) M; 30 minutes) **inhibited** the response of ciliary arteries to Ang II, whereas the AT2-receptor ligand CGP 42112 B (10(-7) to 10(-8) M) was ineffective. In the perfused porcine **eye**, valsartan restored the decrease in flow to Ang II. CONCLUSIONS. **Angiotensins** play an important regulatory role in the porcine ophthalmic microcirculation through AT1-receptors. ACE-**inhibitors** prevents the effects of Ang 1 and augment endothelium-dependent relaxation to bradykinin, which releases nitric oxide through B2 receptors.

L20 ANSWER 22 OF 37 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 96058770 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8590256
TITLE: Effect of **captopril** on ocular irritative response to topical neutral formaldehyde and YAG-laser capsulotomy in the rabbit.
AUTHOR: Krootila K; Oksala O; Von Dickhoff K; Palkama A; Uusitalo H
SOURCE: Journal of ocular pharmacology and therapeutics : official

journal of the Association for Ocular Pharmacology and Therapeutics, (1995 Fall) 11 (3) 243-52.
Journal code: 9511091. ISSN: 1080-7683.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960404
Last Updated on STN: 19960404
Entered Medline: 19960325

AB **Angiotensin** converting enzyme (ACE) -**inhibitors** **inhibit** degradation of inflammatory mediators substance P (SP) and bradykinin, which may further stimulate the synthesis of prostaglandins. The resulting **increase** in inflammatory mediators in tissues is suggested to be the reason for the dry cough, involving sensory C-fiber activation, among patients receiving ACE-**inhibitor** therapy. In the present study, the effect of an ACE-**inhibitor**, **captopril**, on ocular irritative responses was studied in the rabbit. Intravenous **captopril** decreased markedly the blood pressure and the intraocular pressure (IOP) modestly. Topical neutral formaldehyde elicits an irritative response in the **eye** mediated through sensory neuropeptides SP and calcitonin gene-related peptide (CGRP). Following topical neutral formaldehyde, the **increase** in IOP and breakdown of the blood-aqueous barrier were **inhibited** by **captopril**, while miosis was not affected. Cyclic AMP (cAMP) content in the aqueous humour was **increased** by **captopril** , and this **increase** was **inhibited** by indomethacin. Following YAG-laser anterior capsulotomy, **captopril** **inhibited** the **increase** in IOP, breakdown of the blood-aqueous barrier and miosis. The present study demonstrates that use of short-term administration of **captopril** prior to sensory nerve stimulation or YAG laser anterior capsulotomy does not **enhance** the ocular responses to these stimuli in the rabbit. In the present study, **captopril** **inhibited** these responses, at least partly by decreasing the blood pressure.

L20 ANSWER 23 OF 37 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:210565 BIOSIS
DOCUMENT NUMBER: PREV199598224865
TITLE: Effects of **captopril** and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure.
AUTHOR(S): Walsh, John T. [Reprint author]; Andrews, Richard; Starling, Rowena; Cowley, Alan J.; Johnson, Ian D. A.; Kinnear, William J.
CORPORATE SOURCE: Div. Cardiovascular Med., Univ. Hospital, Nottingham NG7 2UH, UK
SOURCE: British Heart Journal, (1995) Vol. 73, No. 3, pp. 237-241.
CODEN: BHJUAV. ISSN: 0007-0769.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 1995
Last Updated on STN: 23 May 1995

AB Objectives: To determine the effects of **captopril** and oxygen on sleep quality in patients with mild to moderate cardiac failure. Design: An open observational study. Patients: 12 patients with New York Heart Association class II-III heart failure were studied at baseline. 9 of these patients were then examined at the end of 1 month of treatment with **captopril**; 9 of the patients were separately assessed during a

single night of supplementary oxygen. Main outcome measures: Sleep patterns by polysomnography, overnight oximetry, and subjective sleep assessment using visual analogue scores. Results: Abnormal sleep was present in all baseline studies. Complete polysomnograms after treatment with **captopril** were obtained in 8 patients. Light sleep (stages 1 and 2) was reduced (mean (SEM) 61%(8)% to 48%(6)% actual sleep time, P lt 0.05) but slow wave (stages 3 and 4) and REM (rapid **eye** movement) sleep **increased** (25%(6)% to 31%(5)%, 14%(2)% to 21%(5)% actual sleep time, P lt 0.05). Apnoeic episodes (242(59) to 118(30), P lt 0.05), desaturation events (171(60) to 73(37), P lt 0.05), and arousals (33(5) to 18(3) P lt 0.01) were reduced. Visual analogue scores of sleep quality **increased** 49(5) to 69(5), P lt 0.01). Complete polysomnograms were obtained in 7 patients treated with oxygen. Light sleep duration was reduced (55% (7)% to 42%(5)% actual sleep time, P lt 0.05) and slow wave sleep **increased** (30%(5)% to 38%(6)% actual sleep time, P lt 0.05). REM sleep duration was not significantly different. Total arousals (33(6)% to 20(2) P lt 0.05), desaturation events (140(33) to 38(10), P lt 0.01), and apnoeic episodes (212(53) to 157(33), P lt 0.05) were reduced. Visual analogue scores of sleep quality were unchanged. Conclusions: **Captopril** and oxygen may **improve** sleep quality and reduce nocturnal desaturation in patients with mild to moderate cardiac failure. **Improved** sleep quality could explain the reduction in daytime symptoms seen after treatment in patients with chronic heart failure.

L20 ANSWER 24 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 94166214 EMBASE
DOCUMENT NUMBER: 1994166214
TITLE: **Angiotensin**-converting enzyme **inhibitors**
.
SOURCE: International Pharmacy Journal, (1994) 8/2 (58-63).
ISSN: 1010-0423 CODEN: IPHJEN
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English; French; German

AB The **angiotensin**-converting enzyme (ACE) **inhibitors** are now established therapies for the treatment of hypertension and heart failure. There are currently nine compounds within the group; more may be licensed. Despite claims of potential advantages of one compound over another, no clinically significant differences in efficacy, either in hypertension or heart failure, have been shown so far. Widespread use of ACE **inhibitors** as first-line antihypertensive therapy is not currently supported by the data available; the British Hypertension Society recommend that first-line use should be reserved for selected patients whose medical history makes the use of conventional first-line therapies inappropriate. ACE **inhibitors** are effective in the treatment of hypertension, producing a satisfactory response in 40-50% of patients when used alone; this may **increase** to 80% if used in combination with other antihypertensives. Quality of life indices may be **improved**, in relation to other therapies, in hypertensive patients treated with ACE **inhibitors**, although the evidence is currently inconclusive. ACE **inhibitors** are of proven benefit in the treatment of heart failure, resulting in symptomatic **improvement** and reduced mortality. Therapy for selected patients at low risk of first-dose hypotension may now be initiated under **supervision** by

GPs. Adverse effects of ACE **inhibitors** are relatively few; they include cough, rash and taste disturbances. Potentially fatal angioedema occurs rarely, as do neutropenia and agranulocytosis. Potassium-sparing diuretics or potassium supplements should not generally be used with ACE **inhibitors**, due to the risk of hyperkalemia. Serum lithium concentrations may rise significantly if an ACE **inhibitor** is added.

L20 ANSWER 25 OF 37 MEDLINE on STN
ACCESSION NUMBER: 94057870 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8239321
TITLE: **Angiotensin**-converting enzyme **inhibitor** treatment for young normotensive diabetic subjects: a two-year trial.
AUTHOR: Chase H P; Garg S K; Harris S; Hoops S; Jackson W E; Holmes D L
CORPORATE SOURCE: Department of Pediatrics, University of Colorado Health Sciences Center, Denver.
CONTRACT NUMBER: 5 MO1 RR0051 (NCRR)
SOURCE: Annals of ophthalmology, (1993 Aug) 25 (8) 284-9. Journal code: 0210137. ISSN: 0003-4886.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19940117
Entered Medline: 19931201

AB Microangiopathy characterizes both diabetic retinopathy and nephropathy. It is currently unclear which diabetic subjects should be treated with **angiotensin**-converting enzyme (ACE) **inhibitors**. A double-blind, placebo-controlled protocol was implemented using **captopril** to treat subjects with Type I diabetes, early diabetic nephropathy (albumin excretion rates, 20-200 micrograms/min), and normal blood pressures. After two years, the final **eye** grades were **improved** in two treated subjects but not in any of the controls. Three control and one treated subject showed worsening of their **eye** grade after two years ($P < .001$, by chi-square test). Significant differences in renal albumin excretion were not seen between the two groups. The distribution of changes in retinal grades in the treatment group compared with the placebo group was **improved** after two years. Studies of larger numbers of patients will be necessary to determine if ACE **inhibitors** should be used routinely in subjects with diabetic retinopathy and to determine which subjects are most likely to respond.

L20 ANSWER 26 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 92179215 EMBASE
DOCUMENT NUMBER: 1992179215
TITLE: **Angiotensin** converting enzyme **inhibitors** versus digoxin for the treatment of congestive heart failure.
AUTHOR: Crozier I.; Ikram H.
CORPORATE SOURCE: Cardiology Department, The Princess Margaret Hospital, Canterbury Area Health Board, Private Bag,Christchurch, New Zealand

SOURCE: Drugs, (1992) 43/5 (637-650).
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Angiotensin** converting enzyme (ACE) **inhibition** and digoxin may be used in the management of heart failure. Digoxin **increases** myocardial contractility in vitro, and has a modest but durable beneficial effect in congestive heart failure due to impaired left ventricular systolic function. ACE **inhibitors** have clear beneficial effects in all grades of heart failure and, in addition, modify the natural history and reduce mortality. Comparative studies in mild to moderate heart failure reveal a tendency towards greater benefits and tolerability of ACE **inhibitors** over digoxin. ACE **inhibition** is indicated, in conjunction with diuretic therapy, for all grades of heart failure. Digoxin is best reserved for patients with atrial fibrillation and a rapid ventricular response, and for those whose heart failure is not controlled with an ACE **inhibitor** plus a diuretic. In patients with heart failure following myocardial infarction, digoxin is of modest benefit. Digoxin should be administered slowly and carefully to avoid acute vasoconstriction and toxicity. **Provisional** data suggest ACE **inhibitors** are also beneficial in these patients. However, the results of clinical trials presently in progress are required to clarify their role following myocardial infarction.

L20 ANSWER 27 OF 37 MEDLINE on STN
ACCESSION NUMBER: 92238629 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1570931
TITLE: **Angiotensin**-converting enzyme **inhibitor** therapy and diabetic retinopathy.
AUTHOR: Jackson W E; Holmes D L; Garg S K; Harris S; Chase H P
CORPORATE SOURCE: Department of Ophthalmology, University of Colorado Health Sciences Center, Denver 80262.
CONTRACT NUMBER: RR69 (NCRR)
SOURCE: Annals of ophthalmology, (1992 Mar) 24 (3) 99-103.
Journal code: 0210137. ISSN: 0003-4886.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920612
Last Updated on STN: 19920612
Entered Medline: 19920528

AB This pilot project suggested that **angiotensin**-converting enzyme (ACE) **inhibitors** may have an effect on delaying or reversing diabetic retinopathy. One patient who had Grade 5 (preproliferative) retinopathy **improved** to Grade 2 (microaneurysms only) after two years of treatment. Of the 450 patients followed in our **eye** and kidney clinic, no other patient showed a similar reversal from Grade 5 retinopathy without treatment. **Improvement** by one or more grades was seen in three other patients with variable grades of retinopathy after a mean of 3.3 years of treatment. **Improvement** was not related consistently to a decrease in blood pressure (0 of 4), better glycemic control (2 of 4), or reduction in albumin excretion rate

(0 of 4). Proper double-blind controlled studies are needed to prove the effect of ACE **inhibitors** on diabetic microangiopathy of the **eye**.

L20 ANSWER 28 OF 37 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1991:263736 BIOSIS
DOCUMENT NUMBER: PREV199140126616; BR40:126616
TITLE: **ANGIOTENSIN** CONVERTING ENZYME **INHIBITORS** CEI AMELIORATE **INCREASED** VASCULAR LEAKAGE OF ALBUMIN IN **EYES** OF DIABETIC RATS.
AUTHOR(S): IDO Y [Reprint author]; CHANG K; ALLISON W S; TILTON R G; WILLIAMSON J R
CORPORATE SOURCE: DEP PATHOL, WASHINGTON UNIV SCH MED, ST LOUIS, MISSOURI, USA
SOURCE: Investigative Ophthalmology and Visual Science, (1991) Vol. 32, No. 4, pp. 1288.
Meeting Info.: ANNUAL SPRING MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY, SARASOTA, FLORIDA, USA, APRIL 28-MAY 3, 1991. INVEST OPHTHALMOL VISUAL SCI.
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 5 Jun 1991
Last Updated on STN: 16 Jul 1991

L20 ANSWER 29 OF 37 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 90341098 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2199950
TITLE: Focal metabolic effects of **angiotensin** and **captopril** on subregions of the rat subfornical organ.
AUTHOR: Shaver S W; Kadekaro M; Gross P M
CORPORATE SOURCE: Department of Surgery, Queen's University, Kingston, Ontario, Canada.
CONTRACT NUMBER: NS 23055 (NINDS)
SOURCE: Peptides, (1990 May-Jun) 11 (3) 557-63.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19901012
Last Updated on STN: 19901012
Entered Medline: 19900913

AB **Angiotensin** infusion **increased** glucose metabolism in 4 of 7 **subdivisions** of the rat subfornical organ, the effect being stronger in ventromedial compared to dorsolateral zones across the rostrocaudal axis. [Sar1-Leu8]**Angiotensin** II attenuated metabolic responses to intravenous **angiotensin** in all subfornical organ subregions. Brattleboro rats, having high circulating levels of **angiotensin**, displayed greater rates of glucose metabolism than Long-Evans rats in all subregions, differences that were eliminated by **captopril**, an **inhibitor** of **angiotensin** converting enzyme. The studies reveal focal subfornical organ zones where in vivo metabolic activity corresponds to cytoarchitectonic evidence for topographical processing within this **angiotensin**-sensitive structure.

L20 ANSWER 30 OF 37 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 9

ACCESSION NUMBER: 1990:158599 BIOSIS
DOCUMENT NUMBER: PREV199089086017; BA89:86017
TITLE: SIMULTANEOUS PERFUSION OF RAT ISOLATED SUPERIOR MESENTERIC ARTERIAL AND VENOUS BEDS COMPARISON OF THEIR VASOCONSTRICTOR AND VASODILATOR RESPONSES TO AGONISTS.
AUTHOR(S): WARNER T D [Reprint author]
CORPORATE SOURCE: THE WILLIAM HARVEY RES INST, THE MED COLL ST BARTHOLOMEW'S HOSP, CHARTERHOUSE SQUARE, LONDON EC1M 6BQ, UK
SOURCE: British Journal of Pharmacology, (1990) Vol. 99, No. 2, pp. 427-434.
CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Mar 1990
Last Updated on STN: 28 Mar 1990

AB A new isolated perfused preparation is described that allows a direct comparison to be made of the responses of the perfused arterial and retrogradely perfused venous circulations of the rat superior mesenteric vascular bed. In experiments comparing the responses of the intact arterially perfused mesentery and small intestine to those of the same preparation following removal of the intestine and **division** of the circulations, the **increases** in perfusion pressure produced by arginine-vasopressin (30 pmol) and noradrenaline (1 nmol) were retained by the arterial circulation and those induced by **angiotensin** II (30 pmol) by the venous circulation. Endothelin-1 (30 pmol) constricted both portions of the vasculature but the prolonged nature of its response was asssociated with only the venous vessels. In the simultaneously perfused arterial and venous preparation arginine vasopressin (3-100 pmol) was a selective constrictor of the arterial circulation and **angiotensin** II (3-100 pmol) of the venous circulation. In addition, noradrenaline (0.3-10 nmol), 5-hydroxytryptamine (0.3-10 nmol) and KCl (1-60 μmol) were more active as constrictors of the arterial than the venous vessels, and U46619 (10-300 pmol) a more active constrictor of the venous than the arterial vessels. Endothelin-1 (3-100 pmol) constricted both the arterial and venous portions of the vasculature but was significantly longer acting as a venoconstrictor than an arterioconstrictor. **Angiotensin** I (300 pmol) caused constrictions of the venous circulation which were dependent upon the presence of **angiotensin** converting enzyme for **captopril** (10 μM) abolished constrictions caused by **angiotensin** I but not by **angiotensin** II. In preparations preconstricted by U46619 (0.3-3 μM), acetylcholine (0.01-100 nmol), bradykinin (0.001-1 nmol), sodium nitroprusside (0.01-10 nmol) or isoprenaline (1-100 pmol) produced dose-related dilatations of both the arterial and the venous vasculatures, whereas adenosine diphosphate (ADP, 0.01-100 nmol) caused dose-dependent dilatations of the arterial circulation but principally constrictions of the venous circulation. The dilatations caused by acetylcholine and bradykinin in both portions of the circulation, and by ADP in the arterial circulation, were endothelium-dependent as they were **inhibited** by gossypol (3 μM), whereas dilatations to sodium nitroprusside were not. This preparation allows the responses of the arteries and veins of a single perfused mesenteric bed to be compared. In addition, with this preparation it is possible to demonstrate that veins, as well as arteries, show significant endothelium-dependent relaxations. It is concluded that the venous portion of the vasculature is significantly involved in the responses of the intact circulation.

L20 ANSWER 31 OF 37 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 90300257 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2163428
TITLE: Prostaglandins mediate the ocular hypotensive action of the **angiotensin** converting enzyme **inhibitor** MK-422 (**enalaprilat**) in African green monkeys.
AUTHOR: Lotti V J; Pawlowski N
CORPORATE SOURCE: Department of New Lead Pharmacology, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania.
SOURCE: Journal of ocular pharmacology, (1990 Spring) 6 (1) 1-7. Journal code: 8511297. ISSN: 8756-3320.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 19900907
Entered Medline: 19900808

AB MK-422 (**enalaprilat**) (0.0005-0.5%) significantly reduced intraocular pressure (IOP) in African Green monkeys. Studies utilizing unilateral instillation of MK-422 and its inactive R-isomer indicated a local site of action within the **eye** which is dependent upon **inhibition** of **angiotensin** converting enzyme, also known as kininase II. Tonography showed a small **increase** (21%) in conventional aqueous humor outflow facility which did not entirely account for the IOP lowering effect of MK-422. Pretreatment with indomethacin or pilocarpine specifically attenuated the ability of MK-422 to lower IOP suggesting that biosynthesis of prostaglandins and uveoscleral outflow pathways are important in mediating the ocular hypotension. The data indicate that MK-422 may lower IOP in monkeys by virtue of its ability to prevent the breakdown of bradykinin and thereby promote the formation of endogenous prostaglandins in the **eye**.

L20 ANSWER 32 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 89248412 EMBASE
DOCUMENT NUMBER: 1989248412
TITLE: Bronchial effects of alpha2-adrenoceptor agonists and of other antihypertensive agents in asthma.
AUTHOR: Xuan A.T.D.; Lockhart A.
CORPORATE SOURCE: Laboratoire d'Explorations Fonctionelles, Hopital Cochin, 75014 Paris, France
SOURCE: American Journal of Medicine, (1989) 87/3 C (34S-37S). ISSN: 0002-9343 CODEN: AJMEAZ
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The respective prevalence of hypertension and asthma is sufficient for their combined existence to be far from rare. The effects of certain antihypertensive drugs, e.g., alpha2-adrenoceptor agonists, on the brnchi may be either harmful or beneficial. When inhaled, alpha2-agonists reduce the immediate bronchial response to allergens, whereas when ingested they aggravate the bronchial response to histamine and all the more so when

their effect on the central nervous system is greater. Therefore, there has been much interest in agents such as the new oxazoline derivative, rilmenidine, which has less central effects than clonidine, an imidazoline compound of reference. Calcium antagonists **inhibit** smooth muscle contraction and release of mast cell inflammatory mediators. In asthmatic subjects, their short-term administration leads to a modest **improvement** in spontaneous bronchial obstruction, has only a partial protective action against various nonspecific or allergenic stimuli, and slightly reinforces the beneficial effect of beta2-agonists. Beta-adrenoceptor antagonists aggravate bronchial obstruction and nonspecific bronchial hyperreactivity in asthmatic subjects. These harmful effects are dose-dependent, have even been reported after the administration of **eyedrops**, and are common to all beta-blockers. **Angiotension**-converting enzyme **inhibitors** **increase** bronchial hyperreactivity in patients who develop cough during treatment and may, in certain cases, worsen or even induce asthma, probably by opposing inactivation by hydrolysis of tachykinins and of bradykinins.

L20 ANSWER 33 OF 37 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 88244367 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2897990
TITLE: The cardiovascular responses to sequential **inhibition** of alpha-adrenoceptors, the renin-**angiotensin** system and vasopressin in rats with adrenal regeneration hypertension.
AUTHOR: Foulkes R; Gardiner S M; Bennett T
CORPORATE SOURCE: Department of Physiology and Pharmacology, Queen's Medical Centre, Nottingham, UK.
SOURCE: Journal of hypertension, (1988 Apr) 6 (4) 305-10.
Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880718

AB The cardiovascular responses to selective alpha 1- and alpha 2-adrenoceptor antagonism (with prazosin and idazoxan, respectively) were assessed in rats 4 weeks after unilateral nephro-adrenalectomy, contralateral adrenal enucleation and the **provision** of a 1% NaCl solution as drinking fluid (AEN rats) and in sham-operated (SON) rats. Measurements were made between 0700 and 1000 h and between 1400 and 1700 h, since we have previously shown that resting blood pressures (BPs) in AEN rats are higher in the morning than in the afternoon. Following prazosin administration (morning or afternoon), BP fell to similar levels in both SON and AEN rats. Idazoxan, given 20 min after the start of prazosin infusion, caused similar transient falls in BP in all four groups of rats. Following the subsequent additional antagonism of **angiotensin** II (Ang II) production (with **captopril**) and vasopressin (V1) receptors [with d(CH2)5DAVP], BP in AEN rats studied in the morning was higher than in SON rats at that time of day, and higher than in AEN rats studied in the afternoon. These findings suggest than an additional underlying mechanism capable of **increasing** BP exists in AEN rats studied in the morning.

L20 ANSWER 34 OF 37 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 87312538 MEDLINE

DOCUMENT NUMBER: PubMed ID: 3041080
TITLE: Familial hyper-**angiotensin** converting enzyme (ACE)-emia: increased production of ACE by monocyte-macrophage.
AUTHOR: Okabe T; Fujisawa M; Watanabe J; Yotsumoto H; Takaku F
SOURCE: Japanese journal of medicine, (1987 May) 26 (2) 140-6. Journal code: 0247713. ISSN: 0021-5120.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (CASE REPORTS) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198710
ENTRY DATE: Entered STN: 19900305 Last Updated on STN: 19900305 Entered Medline: 19871020

AB We report here a familial clustering of elevated serum **angiotensin** converting enzyme (ACE) levels. The patient was a 58-year-old Japanese female. She had been in excellent health until the age of 45, when she noticed a decrease in **visual acuity** of her left **eye**. Despite intensive therapy under the diagnosis of occulusion of the central retinal vein, she lost her **visual acuity** at the age of 45. Thereafter, she has been in excellent health. The only abnormality found in this case has been a markedly elevated level of serum ACE (625 n mol/min/ml; normal range; 22-40 n mol/min/ml of serum). Her blood pressure was within normal limits (140/80 mmHg). There was no evidence for the diagnosis of sarcoidosis, Gaucher's disease, leprosy, hyperthyroidism, diabetic retinopathy, or liver disease. One of her two sisters also showed a marked **increase** in serum ACE activity (303 n mol/min/ml), and remarkably high levels of serum ACE (276 and 294 n mol/min/ml) were demonstrated in both of two sons of this sister. All the members of this family have been in excellent health. The serum ACE activity was activated by chloride and cobalt ions, and **inhibited** by EDTA, **captopril** and rabbit antiserum to purified human plasma ACE. Thus, our study showed a familial clustering of "hyper-ACE-emia", and the disorder appears to have been inherited as an autosomal dominant trait.

L20 ANSWER 35 OF 37 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 86159001 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3513778
TITLE: General pharmacology of the novel **angiotensin** converting enzyme **inhibitor** alacepril. 2nd communication: Effects on central nervous and sensory systems and on the other functions.
AUTHOR: Matsuno Y; Hori H; Oka M; Nakamura H; Ito T; Kadokawa T
SOURCE: Arzneimittel-Forschung, (1986) 36 (1) 62-8. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 19900321 Last Updated on STN: 19900321 Entered Medline: 19860421

AB The effects of 1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine (alacepril, DU-1219), an orally active **angiotensin** converting enzyme **inhibitor**, on the central nervous and sensory systems and on several other functions were compared with those of

captopril in the experimental animals. Alacepril at the high oral dose of 600 mg/kg prolonged the hexobarbital sleeping time and potentiated the reserpine-induced hypothermia in mice. However, alacepril at the same dose did not affect the general behavior, convulsions induced by maximal electroshock, pentetrazol and strychnine, active avoidance in mice and body temperature in rats. In addition, alacepril (200 mg/kg i.v.) has little effect on general behavior in mice. **Captopril** at over 107 mg/kg p.o. produced **eyelid** closure and at 320 mg/kg prolonged the hexobarbital sleeping time. A metabolite of alacepril, desacetylalacepril (DU-1227) (200 mg/kg i.v.), caused salivation in mice. Alacepril and DU-1227 at 60 mg/kg i.v. were without effect on flexor reflex and spontaneous electroencephalogram (EEG) in cats, while **captopril** at the equimolar dose depressed the flexor reflex and showed a tendency to **increase** the beta 2-band relative power of the cortical EEG. Alacepril and **captopril** neither affected the writhing syndrome induced by acetic acid nor that by phenylquinone in mice. Local anesthetic and irritant activities in rabbits and effect on neuromuscular junction in anesthetized rats were not observed with the two compounds. Alacepril at the oral dose of 0.1 mg/kg potentiated the carrageenin-induced edema in rats. However, the effect was one third that of **captopril**. Alacepril and **captopril** did not affect the **increased** vascular permeability by acetic acid in mice.(ABSTRACT TRUNCATED AT 250 WORDS)

L20 ANSWER 36 OF 37 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 81225295 EMBASE
DOCUMENT NUMBER: 1981225295
TITLE: [**Captopril** and diuretics in the treatment of hypertensive patients with renal failure]. BEHANDLUNG NIERENINSUFFIZIENTER HYPERTONIKER MIT **CAPTOPRIL** UND DIURETIKA.
AUTHOR: Rieger J.; Kirchertz E.J.; Groene H.J.
CORPORATE SOURCE: Med. Klin., Univ., 3400 Gottingen, Germany
SOURCE: Therapiewoche, (1981) 31/34 (5290-5299). CODEN: THEWA6
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
028 Urology and Nephrology
006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: German
SUMMARY LANGUAGE: English

AB 25 renally insufficient patients with therapy-resistant hypertension were treated for 5 through 8 days under hospital **supervision** and subsequently as ambulatory patients with the converting-enzyme **inhibitor captopril** and furosemide. An adequate decrease in blood pressure was observed in all cases; plasma **angiotensin** converting enzyme activity was markedly reduced, plasma renin activity **increased**, and aldosterone concentration fell initially but then rose during further treatment. On account of the latter, the majority of the patients required either potassium substitution or aldosterone antagonists. The following side effects were observed: leucopenia, in combination with immunosuppressive therapy, aneugesia, exanthema and deterioration of kidney function. These findings are discussed with respect to the current literature. In addition, an attempt is made to evaluate recommended doses, and the authors opinion is expressed on the necessary conditions for therapy when **captopril** is indicated.

L20 ANSWER 37 OF 37 JAPIO (C) 2004 JPO on STN
ACCESSION NUMBER: 2001-002587 JAPIO
TITLE: AGENT FOR IMPROVING HGF PRODUCTION
INVENTOR: YASUDA SATOSHI
PATENT ASSIGNEE(S): SOOSEI:KK
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2001002587	A	20010109	Heisei	A61K045-00

APPLICATION INFORMATION
STN FORMAT: JP 1999-169849 19990616
ORIGINAL: JP11169849 Heisei
PRIORITY APPLN. INFO.: JP 1999-169849 19990616
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2001

AN 2001-002587 JAPIO
AB PROBLEM TO BE SOLVED: To obtain the subject **improving** agent having remarkable HGF production **improving** action and useful as a therapeutic agent for various diseases by including an **angiotensin** converting enzyme(ACE) **inhibitor** or an **angiotensin** II receptor agonist.
SOLUTION: This **improving** agent comprises at least one kind selected from a group comprising an ACE(**Angiotensin**-converting enzyme) **inhibitor** and an **angiotensin** receptor antagonist (e.g. losartan or TCV-116) and is preferably used for treatment of liver diseases, renal diseases, skin diseases, blood diseases, **eye** diseases, lung disease, gastroduodenal diseases, cancer diseases, canber-related diseases, ischemic diseases or arterial diseases of heart or extremity, bone diseases and central nervous diseases. For example, SH group-based ACE **inhibitor** such as **captopril** or alacepril, a COOH group-based ACE **inhibitor** such as lisinopril or enalapril, a P-containing group-based ACE **inhibitor** such as temocapril.

Inventor Search

=> d ibib abs hitstr l3 1-1

L3 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:900442 HCAPLUS
DOCUMENT NUMBER: 134:37048
TITLE: Neuroprotective and retinoprotective ophthalmologic medicines
INVENTOR(S): **Rekik, Raouf**
PATENT ASSIGNEE(S): Rekik, Elyes Ben Mohamed Raouf, Fr.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000076499	A2	20001221	WO 2000-FR1679	20000616
WO 2000076499	A3	20010517		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2794975	A1	20001222	FR 1999-15359	19991206
BR 2000011714	A	20020305	BR 2000-11714	20000616
EP 1185255	A2	20020313	EP 2000-951603	20000616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200103665	T2	20021021	TR 2001-20010366520000616	
JP 2003501461	T2	20030114	JP 2001-502832	20000616
FR 2826276	A1	20021227	FR 2001-8136	20010620
NO 2001006088	A	20020212	NO 2001-6088	20011213

PRIORITY APPLN. INFO.:

TN 1999-99122	A	19990616	
FR 1999-15359	A	19991206	
WO 2000-FR1679	W	20000616	

AB The invention concerns a neuroprotective and retinoprotective medicine, whereof the active principle is selected among a group of compds. consisting of ramipril, ramiprilat or any other ramiprilat derivative capable of releasing it in the organism whereto it is administered. Said medicine is used for prevention, or even for improving visual acuity and visual field in normal subjects, as well as for treating ophthalmol. pathologies involving a vascular factor, in particular glaucomatous neuropathy, degenerative choriopathy of strong myopia, age-related maculopathy, serous central chorioretinopathy, hereditary dystrophy of the retina and retinal venous occlusions. It almost invariably improves the visual function (acuity and visual field). Efficacy of 1.25 mg oral ramipril in the treatment of patients suffering from retinitis pigmentosa and dystrophy pseudo-vitelliform of adult was shown.

IT **9015-82-1**, Angiotensin converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; neuroprotective and retinoprotective ophthalmol. medicines)
RN 9015-82-1 HCAPLUS
CN Carboxypeptidase, dipeptidyl, A (9CI) (CA INDEX NAME)

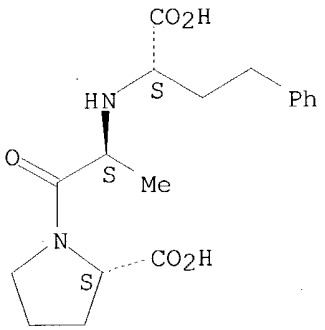
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **76420-72-9**, Enalaprilat **87269-97-4**, Ramiprilat
87333-19-5, Ramipril
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective and retinoprotective ophthalmol. medicines)

RN 76420-72-9 HCAPLUS

CN L-Proline, N-[(1S)-1-carboxy-3-phenylpropyl]-L-alanyl- (9CI) (CA INDEX NAME)

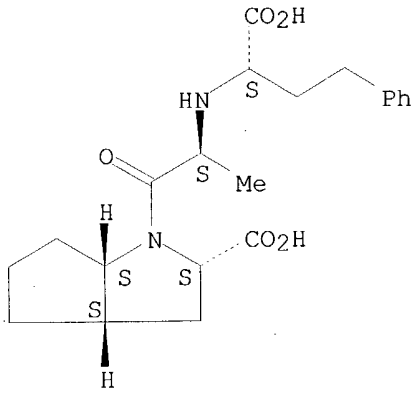
Absolute stereochemistry.



RN 87269-97-4 HCAPLUS

CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,6aS)- (9CI) (CA INDEX NAME)

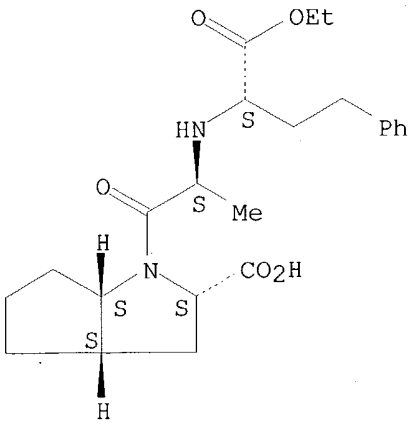
Absolute stereochemistry.



RN 87333-19-5 HCAPLUS

CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,6aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


O
OEt
HN
S
Ph
O
S
Me
H
N
CO2H
S
S
S
H